REMARKS

Applicants have carefully studied the Final Office Action mailed on April 20, 2004, which issued in connection with this application. The present response is intended to be fully responsive to all points of rejection raised by the Examiner and is believed to place the claims in condition for allowance. Favorable reconsideration and allowance of the present claims are respectfully requested.

Pending Claims

Claims 2-22 were pending and at issue in the application. Claims 7-8, 10-11 and 15-22 have been withdrawn from consideration until the linking claims are found allowable. Claims 2-3, 5-6 and 12-13 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. Claims 2-6 and 12-14 have been rejected under 35 U.S.C. § 102(b) as being anticipated by prior art.

Claims 3-4 and 13-14 have been canceled without prejudice or disclaimer.

New independent claim 23 has been added. Support for this new claim can be found, for example, in the original claims 2 and 6-11, at page 13, lines 15-24, page 17, line 22 - page 18, line 16, page 26, lines 9-17, page 29, line 28 - page 30, line 6, and Example 1 (especially page 35, lines 11-30 and pages 38-41 including Table I at pages 40-41).

Claim 2 has been amended by introducing the recitation "nucleic acid is derived from HCV-derived fragment I377/NS3-3'UTR (SEQ ID NO: 1)". Support for this recitation can be found, for example, in the original claim 6, at page 13, lines 18-22, page 17, line 24 - page 18,

line 25, page 26, lines 9-11, Example 1 (in particular, page 34, lines 19-24 and page 38, lines 2-11), and Figure 3. Claim 2 has been further amended by introducing the recitation "when transfected into a human hepatoma cell line Huh-7". Similarly, claim 12 has been amended by introducing the recitation "is derived from a human hepatoma cell line Huh-7". Support for these recitations can be found, for example, in the original claims 4, 12 and 14-19, at page 14, lines 24-32, page 18, lines 12-16, page 28, line 28 - page 29, line 15, and Example 1.

Claims 5-6, 12 and 15-19 have been amended to correct dependency.

Claims 6-11 and 20 have been amended to correct formal defects.

No new subject matter has been added as a result of these amendments, no new search is required, and no new issues are raised. Applicants note for the record that the present amendments are made solely to expedite the prosecution and not as an admission of lack of enablement or anticipation. Applicants reserve the right to pursue canceled subject matter in a continuing application.

Restriction Requirement

Applicants respectfully acknowledge that the Examiner has modified the Restriction Requirement to rejoin claims 4, 6, 9, 12-14, and 17 with claims 1-3 and 5 for examination in the present application. Applicants further acknowledge the Examiner's statement at page 3 of the Office Action that claims 7-8, 10-11 and 15-22 will be rejoined with the claims currently under examination upon allowance of the linking claims.

35 U.S.C. § 112, First Paragraph Rejections

In the Action, claims 2-3, 5-6 and 12-13 stand rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. According to the Examiner, the present specification is enabling for an isolated nucleic acid molecule encoding HCV genome I377/NS3-3'UTR and having, as a result of a long-term propagation in culture, mutations that enable it to replicate efficiently in Huh-7 cell line. However, the Examiner contends that this does not reasonably provide enablement for a genus of nucleic acid molecules encoding any full or partial HCV genome that is able to replicate efficiently when transfected into any or all susceptible cell lines, as in claims 3 and 13, and without reducing the growth rate of such cell lines by more than 10-fold. The Examiner further contends that pending claims 2-3 and 5 read on any or all heterogeneous HCV variants and the specification does not teach how to construct each of these variants. The Examiner also states that it is unpredictable that every cell line is suitable for growing the HCV replicon due to heterogeneity and toxicity of HCV RNA, and that mutations in HCV that reduce toxicity are unpredictable due to the large size of HCV genome and high rate of spontaneous mutation.

As claims 3 and 13 have been canceled, the rejection of these claims is rendered moot. Claims 2 and 12 have been amended to recite only a transfected Huh-7 human hepatoma cell line and cell lines derived from the Huh-7 cell line, respectively. New claim 23 also recites only the Huh-7 cell line. Claims 5 and 6 as amended depend from claim 2 or 23. Accordingly, the rejection with respect to non-enablement of other susceptible cell lines is believed to be overcome. However, as noted above, the present amendments are made solely to expedite the prosecution and not as an admission of lack of enablement. Applicants reserve the right to pursue canceled subject matter in a continuing application.

The rejection of claims 2, 5-6 and 12 based on the unpredictability of HCV variants is respectfully traversed. As understood, this rejection is centered around the Examiner's belief that (1) specification has to but does not teach how to construct each of the claimed heterogeneous HCV variants and (2) while the method for selecting the susceptible cell line for propagating a cell harboring HCV replicon is well known in the art, HCV toxicity and the spontaneous mutation rate makes it unpredictable which mutants become selected (see Section 4 at page 4 of the Office Action). Applicants believe these are erroneous assumptions and address them in detail below.

First, applicants note that claim 2 (as amended) and new claim 23 are directed to a very specific class of HCV-derived nucleic acid sequences which can be generated from I377/NS3-3'UTR (SEQ ID NO: 1), using a well-defined and novel selection scheme of the present invention. This scheme takes advantage of the fact that, when transfected into Huh-7 cells, HCV-derived fragment I377/NS3-3'UTR (SEQ ID NO: 1) behaves as a "toxic" agent and decreases the growth rate of these cells by about 99% (see, *e.g.*, page 39, lines 16-30 of the instant specification and Lohmann *et al.*, Science, 1999, 285:110-113). The novel selection scheme disclosed in the present application and recited in claim 23 works by allowing the growth of only those Huh-7 cells that harbor HCV-derived fragments I377/NS3-3'UTR that have acquired at least one mutation in the HCV sequences of SEQ ID NO: 1[1]. Further, these are mutations which decrease the "toxicity" of the original fragment (a so-called "adaptive" mutations). By setting the concentration of the selective agent (about 1 mg/ml G418) and the length of the selection process (about three weeks of G418 selection followed by at least two more weeks of passaging about 1-2 times a week), the invention ensures that the cells that end up

[1] *E.g.*, at page 13, lines 15-24, page 17, line 22 - page 18, line 16, page 26, lines 9-17, page 29, line 28 - page 30, line 6, and Example 1 (especially page 35, lines 11-30 and pages 38-41 including Table I at pages 40-41).

growing after the selection are only those cells that harbor HCV-derived fragments containing "adaptive" mutations. Neither the original I377/NS3-3'UTR fragments, nor any of the fragments that harbor "non-adaptive" mutations (*i.e.*, those mutations that do not decrease the "toxic" effect upon the host cell growth) are present in any of the growing cells after the selection. In other words, the selection results in generation of a specific class of I377/NS3-3'UTR-derived mutant fragments that have only mutations characterized by a defined property, not all possible mutations. Claims 2 and 23 further specify that these mutations occur in the HCV sequences of I377/NS3-3'UTR. The nature of the present selection methodology is precisely that one does not need to know in advance specific HCV regions where the "adaptive" mutations encompassed by the present claims needs to occur. The selection works by eliminating all nucleic acids that do not possess the "adaptive" mutations.

As exemplified by the sequenced selected mutant fragments HCVR2 (SEQ ID NO: 2), HCVR8 (SEQ ID NO: 3), HCVR9 (SEQ ID NO: 4), HCVR22 (SEQ ID NO: 5), and HCVR24 (SEQ ID NO: 6) (recited in claims 7-11 and disclosed, *e.g.*, at pages 40-41), the "adaptive" mutations can occur in various parts of HCV genome. Based on this fact, the large size of HCV genome and high rate of HCV spontaneous mutagenesis, the Examiner concludes that it is very unpredictable which mutations will be selected. Applicants respectfully submit that, in contrast to the Examiner's assertion, the structural variety of the sequenced "adaptive" mutants does not imply that the additional mutations that can be obtained using the selection scheme of the present mutation are too diverse to be properly enabled by the present specification. These mutations have a very specific property that uniquely unites all of them, *i.e.*, to decrease the "toxicity" of HCV-derived fragment for the host cell. As specified in the Applicants' response to the previous Office Action, nothing in the current law or patent practice requires that when a group of nucleic acid molecules is claimed, the structure of each one of them has to be provided in the form of a

specific nucleic acid sequence[2]. A detailed disclosure of distinguishing properties of the claimed molecules (*i.e.*, growth properties of the resulting selected clones as disclosed, *e.g.*, at page 39, lines 23-25 and in Figure 5) taken together with the detailed disclosure of the method for obtaining them (*i.e.*, the selection scheme as disclosed in the present specification (see above)) provides a sufficient enablement for the whole genus.

The present application goes even further than this standard by providing five specific examples of sequences (*i.e.*, HCVR 2, 8, 9, 22, and 24) that represent the species of the claimed genus. As noted in Applicants' response to the previous Office Action, in light of the current law and patent practice, the disclosure of such specific nucleic acid molecules provides by itself a sufficient number of examples of the nucleic acid molecules to enable a generic claim[3].

In the anticipation rejection (Section 10, page 6 of the Office Action), the Examiner argues that the growth rate limitation is of no help, because the growth rate of a cell right after transfection and the growth rate of an established clone are not comparable. In response, applicants note that the growth rate limitation as recited in claims 2 and 23 is a "growth rate which is not more than 10-fold lower than the growth rate of the Huh-7 cell line prior to transfection". Accordingly, in contrast to the Examiner's assertion, the growth rate of the

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[2] See also *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963), in which the court noted: "From the standpoint of patent law, compound and all of its properties are inseparable; they are one and the same thing. ... [T]he patentability of the thing does not depend on the similarity of its formula to that of another compound but on the similarity of the former compound to the latter. There is no basis in law for ignoring any property in making such a comparison." Cited in MPEP Section 2141.02.

[3] *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 & n.23 (Fed. Cir., 1991); *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971); *Application of Angstadt*, 537 F.2d 498, 502-503, 190 USPQ 214, 218 (CCPA 1976); *In re Rasmussen*, 650 F.2d 1212, 1215, 211 USPQ 323, 326 (CCPA 1981); *In re Goffe* (542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976); section 164.03 of MPEP.

"adapted" clones encompassed by the present claims is compared only to the Huh-7 cell line prior to transfection and not right after the transfection. When comparing the growth rate, selected "adapted" clones and naïve Huh-7 cells were used at the same cell density (see, *e.g.*, Figure 5 and page 39, lines 23-25).

Applicants further note that, in contrast to the Examiner's statement at page 4 of the Office Action (Section 4), the method for selecting efficiently replicating HCV-derived nucleic acid molecules and susceptible cell clones were not known in the art at the time the present application was filed (see, *e.g.*, articles published after the filing date of the present application, which acknowledge the importance and novelty of the selection of "adaptive" mutants)[4]. It is precisely the need for developing a selection scheme for efficiently replicating HCV-derived nucleic acid molecules (which are not "toxic" for their host cells) that drove the applicants to the present invention. The selection scheme disclosed in the application and incorporated in new claim 23 is one of the features that distinguish the present invention from the prior art.

Applicants further respectfully submit that the test for enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). The fact that experimentation may be complex does not necessarily make it undue. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983). *See*, also, *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The selection methodology disclosed in the present application is novel. It is described in

[4] See, *e.g.*, Lohmann *et al.*, J. Virol., 75: 1437-1449, 2001, Blight *et al.*, Science, 290: 1972-1974, December 2000, and Marshall, Science, 290: 1870-1871, December 2000, submitted together with the response to the previous Office Action.

the present specification in detail, so that applying it to obtain additional HCV-derived nucleic acids encompassed by the present claims would not require more than routine experimentation from any person of ordinary skill in the art. The selection steps of the present invention can be performed with relative ease, without undue experimentation, and with a reasonable expectation of success. It is also routine to sequence the adaptive mutants. Accordingly, a person of ordinary skill can make the mutants of claim 2 or 23 by following the guidance in the specification.

In light of the above-presented standards and arguments, it is believed that the present application provides an adequate enablement for the full range of nucleic acids and cell lines encompassed by claims 2, 5-6, 12, and 23. Accordingly, the rejection under 35 U.S.C. § 112, first paragraph, is believed to be overcome and withdrawal is kindly requested.

35 U.S.C. § 102(b) Rejections

A. Lohmann *et al.*

In the Office Action, the Examiner has rejected claims 2-6 under 35 U.S.C. § 102(b) as being anticipated by Lohmann *et al.*, Science, 1999, 285:110-113 (hereinafter "Lohmann *et al.*").

As claims 3-4 have been canceled, the rejection of these claim is rendered moot. With respect to claims 2, 5-6 and new claim 23, the rejection is respectfully traversed.

In the Action (Section 8, page 5), the Examiner contends that the structural differences between the nucleic acid sequences of the present invention and the nucleic acid sequence of

Lohmann *et al.* are not recited in the present claims. Applicants respectfully disagree and note that claims 2 and 23 recite that the nucleic acid of the present invention "contains at least one mutation in the HCV sequence of HCV-derived fragment I377/NS3-3'UTR (SEQ ID NO: 1)". Lohmann *et al.* disclose only SEQ ID NO: 1 but does not disclose or suggest any derivatives of this sequence containing mutations. As specified in the applicants' response to the previous Office Action, Lohmann *et al.* also do not disclose or suggest to incubate their clones longer than usual, and under specific selection conditions, to achieve the production of "adapted" HCV clones encompassed by the present claims. On the contrary, they teach away from the present invention by stating in the last column of the article (page 112) that

> "[H]igh-level replication may reflect an adaptation of the replicon to the host cell. As such adaptation would require one or several mutations, formation of an adapted replicon would be rare. However, this possibility is unlikely for two reasons: first, sequence analysis of several replicons recloned from two different cell clones did not reveal consistent mutations; second, upon serial passage of the replicons in naïve Huh-7 cells, we did not observe a significant increase of the number of colonies." (emphasis added).

In Section 9 (page 5) of the Office Action, the Examiner states that Lohmann *et al.* already had the same clones with same sequence structure characteristics as the claimed nucleic acids. The Examiner bases this conclusion on the fact that (i) the present specification discloses that the applicants used the HCV replicon taught by Lohmann *et al.* to do the transfection and (ii) the HCV replicons used by Lohmann *et al.* exhibit a homology between 99.6% to 99.9% to that of the claimed nucleic acid molecules. In response, applicants respectfully submit that, while the HCV-derived fragment I377/NS3-3'UTR (SEQ ID NO: 1) taught by Lohmann *et al.* was indeed used as a source of starting sequence for transfection in the application, this construct is not encompassed by the present claims. The present claims encompass only nucleic acids which contain at least one mutation in the HCV sequence of HCV-derived fragment I377/NS3-3'UTR

(SEQ ID NO: 1). Accordingly, the present claims expressly exclude the HCV-derived fragment I377/NS3-3'UTR (SEQ ID NO: 1) taught by Lohmann *et al.* The fact that the sequence taught by Lohmann *et al.* is 99.6% to 99.9% homologous to the sequences encompassed by the present claims is irrelevant for the determination of anticipation, because Lohmann *et al.* article does not disclose or suggest any of the "adaptive" mutations encompassed by the present claims or a selection method for generating such mutations.

In Section 10 (page 6) of the Office Action, the Examiner also states that the growth rate limitation is not given patentable weight, because the growth rate of a cell right after transfection and the growth rate of an established clone are not comparable. In response, applicants note that the growth rate limitation as recited in claims 2 and 23 is a "growth rate which is not more than 10-fold lower than the growth rate of the Huh-7 cell line prior to transfection". Accordingly, in contrast to the Examiner's assertion, the growth rate of the "adapted" clones encompassed by the present claims is compared only to the Huh-7 cell line prior to transfection and not right after the transfection. When comparing the growth rate, selected "adapted" clones and naïve Huh-7 cells were used at the same cell density (see, *e.g.*, Figure 5 and page 39, lines 23-25). Applicants further note that, in contrast to the present invention, Lohmann *et al.* do not disclose or suggest to obtain "adapted" clones having the growth rate which is not more than 10-fold lower than the growth rate of the Huh-7 cell line prior to transfection.

It follows, that the present claims are not anticipated by Lohmann *et al.*

B. WO 98/39031 (Rice *et al.*)

In the Office Action, the Examiner has also rejected claims 2-3, 5 and 12-14 under 35 U.S.C. § 102(b) as being anticipated by PCT Publication No. WO 98/39031 (Rice *et al.*).

As claims 3 and 13-14 have been canceled, the rejection of these claim is rendered moot. With respect to claims 2, 5, 12, and new claim 23, the rejection is respectfully traversed.

Similarly to the rejection over Lohmann *et al.*, the Examiner argues that (i) structural differences between the claimed nucleic acids and the prior art are not recited in the present claims and (ii) the limitation of the growth rate of host cells does not have any patentable weight, because the replicons disclosed in WO 98/39031 have the same characteristics as the replicons claimed in the present application.

Applicants respectfully disagree. The requirement for a mutation is expressly a structural difference, readily ascertained. The present claims recite that the nucleic acids of the invention are derived from the recombinant HCV construct I377/NS3-3'UTR (SEQ ID NO: 1) and are different from SEQ ID NO: 1 by at least one mutation. WO 98/39031 does not disclose or suggest the HCV-derived fragment I377/NS3-3'UTR (SEQ ID NO: 1) or any mutants derived therefrom. In fact, as noted in applicants' response to the previous office action, the subsequent articles published by the inventors of WO 98/39031 and their co-workers provide a clear proof that (i) at the time WO 98/39031 was filed (February 26, 1998), they did not possess or even suspect the existence of "adapted" replicons and (ii) it was not until the development of the recombinant HCV construct I377/NS3-3'UTR (SEQ ID NO: 1) disclosed in Lohmann *et al.* (published after the filing date of WO 98/39031) that they were able to obtain their "adapted" replicons.

It follows, that the mutant HCV replicons adapted to grow in culture with high efficiency recited in the present claims and disclosed in the present application cannot be anticipated by WO 98/39031.

In summary, none of the references cited by the Examiner anticipate the present invention. Reconsideration and withdrawal of the anticipation rejection is believed to be in order.

CONCLUSION

Applicants request entry of the foregoing amendments and remarks in the file history of this application. In view of the above amendments and remarks, it is respectfully submitted that claims 2, 5-12 and 15-23 are now in condition for allowance and such action is earnestly solicited. If the Examiner believes that a telephone conversation would help advance the prosecution in this case, the Examiner is respectfully requested to call the undersigned agent at (212) 527-7634. The Examiner is hereby authorized to charge any additional fees associated with this response to our Deposit Account No. 04-0100.

Respectfully submitted,

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Irina E. Vainberg, Ph.D.
Reg. No. 48,008
Agent for Applicant(s)

DARBY & DARBY P.C.
805 Third Avenue
New York, New York 10022
212-527-7700